The 2.0 Á Structure of Human Hypoxanthine-Guanine Phosphoribosyltransferase in Complex with a Transition-State Analog Inhibitor

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Abstract No. shi0961
Beamline(s): **X9B**

The structure of human HGPRT bound to the transition-state analog immucillinGP and Mg2+-pyrophosphate has been determined to 2.0 Å resolution by molecular replacement using data collected at X9B. ImmucillinGP was designed as a stable analog with the stereoelectronic features of the transition state. Bound inhibitor at the catalytic site indicates that the oxocarbenium ion of the transition state is stabilized by neighboring-group participation from MgPPi and O5'. A short hydrogen bond forms between Asp 137 and the purine ring analog. Two Mg2+ ions sandwich the pyrophosphate and contact both hydroxyls of the ribosyl analog. The transition-state analog is shielded from bulk solvent by a catalytic loop that moves approximately 25 A to cover the active site and becomes an ordered antiparallel beta-sheet.